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TOPICAL ANTIFUNGAL DRUGS

Notwithstanding the effectiveness of griseofulvin (McNeil, Ayerst and Schering) as a systemic agent for the treatment of fungous infections of the scalp, nails and skin (The Medical Letter, 2:42, 1960), topical therapy is still valuable either by itself or as an adjunct to griseofulvin therapy; and when they are equally effective, a topical drug is preferred.

TOPICAL PREPARATIONS - The physician must choose from a bewildering variety of topical preparations containing fatty acids, oxyquinolines, dyes, antiseptics and keratolytic drugs. Most of them are effective and safe. Acute, vesicular tinea pedis is best treated with antiseptic soaks (1:5000 potassium permanganate, 1:20 Burow's solution or Alibour's solution [Dalidome - Dome]), along with liberal applications of talc and, after the inflammation has subsided, the application of a fungicidal powder or cream. Only if the infection does not yield to such topical measures should griseofulvin be tried.

In subacute and mild chronic infections, fatty acid preparations in the form of powder, ointment or solution are useful. Some contain propionic and capryllic salts, such as Sopronol (Wyeth), or capryllic salts alone, such as R J Powder (Strasenburgh); others are undecylenic acid preparations (Desenex - Maltbie; Timofax - Burroughs Wellcome, etc.). Iodine compounds, copper undecylenate (Decupryl Cream - Crookes, Barnes; Kudelate Ointment - Ulmer), and oxyquinoline derivatives (Vioform Cream - Ciba; Sterosan Cream - Geigy; and others) are also effective; though the oxyquinolines occasionally cause allergic reactions. Diamthazole dihydrochloride (Asterol - Roche) is effective, but its toxic properties and the absence of any important advantage over other preparations make its use undesirable; Asterol has been known to cause toxic encephalitis in children.

TINEA - Superficial tinea infections involving only small areas of the limbs or trunk will usually respond to topical therapy alone without griseofulvin. A mild nonchronic ringworm infection of the feet will yield to almost any of the drugs if their application is accompanied by improved foot hygiene and the regular use of talc for promoting dryness, and if absorbent cotton socks and nonconstricting aerated shoes are worn. In chronic infections, a cream or ointment containing 3% sulfur is often effective; when the skin is thickened and a keratolytic effect is desired, 3% salicylic acid can be added. Topical antifungal and keratolytic drugs, such as Benzoic and Salicylic Acid Ointment, USP (Whitfield's Oint-

ment), can be used advantageously in conjunction with griseofulvin in Trichophyton rubrum infections of the extremely hyperkeratotic type.

Many persons harbor stubborn fungal infections of the skin for years, apparently from an inherent defect in their immunity mechanisms, a lack of the "serum albumin antifungal factor" or through some defect in their keratin. In such persons topical use of a fungicide following successful griseofulvin therapy keeps the fungus from penetrating too deeply and can often prevent reinfection.

PREVENTION OF REINFECTION - While oral griseofulvin has proved effective in all types of tinea capitis, the use of a topical fungicide on the scalp can help prevent reinfection, particularly when others in the environment are not yet cured. (Even with oral griseofulvin therapy, the hair should be cut regularly; the infected hair fragments should be disposed of carefully since they can spread the infection.) One fungus, tinea versicolor, is totally resistant to griseofulvin, but yields to almost any topical antifungal drug, even that old standby, 20% aqueous sodium thiosulfate (which may be combined in a lotion with 10% each of glycerin and pure alcohol). Tinea versicolor may, however, relapse, and it is usually desirable to continue the use of a topical fungicide for weeks or even months after the infection appears to be cured.

Moniliasis of the skin is also unaffected by griseofulvin but may respond to wet dressings of 1:5000 potassium permanganate or Alibour solution, followed by liberal use of plain talc. Or Methylrosaniline Chloride, USP (gentian violet) 1% may be employed, by itself or after the wet dressings. Castellani's carbolfuchsin paint may also be used, 1/2 or 1/3 strength. A vanishing cream containing nystatin (Mycostatin Ointment - Squibb) is usually effective against superficial moniliasis, and if there is much inflammatory reaction it can be prescribed in combination with topical corticosteroids.

SORBOQUEL

Sorboquel (White Laboratories), a mixture of polycarbophil and an anticholinergic (thihexinol methylbromide), is claimed to be "the first truly effective agent to control the dual problem of diarrhea: too fluid feces, too frequent evacuation."

POLYCARBOPHIL - Polycarbophil, the hydrophilic component of Sorboquel, takes up at least three times as much water as psyllium and Methylcellulose, USP. In a double-blind study by B. D. Pimparker, et al. (Gastroenterology, 40: 397, 1961) on three patients with functional diarrhea and 21 patients with such organic disease as ileitis and ulcerative colitis, both polycarbophil and psyllium mucilloid in doses of 5 Gm. daily decreased the rate of stool passage in about two-thirds of the patients. The authors report, however, that "the cases of diarrhea which failed to respond to the hydrophilic preparations were, with one exception, cases of moderately advanced regional ileitis, ileocolitis, and ulcerative colitis with very watery stools." Hydrophilic preparations appear to have been successful mainly in the milder diarrheas, where significant placebo response might be expected. A placebo group was not employed in the study. In completely uncontrolled trials with Sorboquel at a round-table conference (Amer. J. Dig. Dis., 5: 962, 1960),

good results were obtained in acute diarrheas — which characteristically are self-terminating — and in the irritable-colon syndrome. The drug was least effective in chronic organic diarrhea.

ANTICHOLINERGIC - Thihexinol methylbromide, the anticholinergic component of Sorboquel, was discussed at the same conference by G. Gordon McHardy. In an uncontrolled trial with thihexinol methylbromide in 18 patients with irritable-colon syndrome, 11 were "relieved." Dr. McHardy reported that "when one turns to the chronic diarrheas of organic origin — those related to diverticulitis, for instance — the story is entirely different." Of 14 patients with diverticulitis and diarrhea, 9 obtained no relief whatsoever. In chronic ulcerative colitis, only five of the 12 patients were relieved by the drug. Of eight patients with definite regional enteritis and diarrhea and 5 with pancreatic steatorrhea, none obtained relief. These results are consistent with previous experience with anticholinergic drugs, which are most effective in the irritable-colon syndrome (in which sedatives or placebos are also effective), and least effective in the acute bacterial and viral diarrheas and in the chronic organic diarrheas.

SIDE EFFECTS - Only minor complaints of bloating were noted in the study by Dr. Pimparker's group. Because hydrophilic gels have caused obstruction of the esophagus and large intestine, however, Sorboquel is contraindicated in elderly persons, and in the presence of stenosis anywhere in the gastrointestinal tract.

In summary, Sorboquel, like other hydrophilic gels, may be useful in some instances of mild diarrhea and in the irritable-colon syndrome. That is has any advantage over placebos or sedatives in the treatment of the irritable-colon syndrome, however, has yet to be shown. (See the Medical Letter appraisal of Lomotil, 3:61, Aug. 4, 1961, for a discussion of the treatment of diarrhea.)

VITAMIN K PRODUCTS IN THE CONTROL OF HEMORRHAGE

Vitamin K is promoted and used as a hemostatic agent to prevent or check medical and surgical bleeding regardless of cause, and a large number of vitamin K products, oral and parenteral, are available to physicians. Except for hemorrhage due to prothrombin deficiency, however, these agents are of no value.

The major causes of hypoprothrombinemia and the place of vitamin K in the management of the resulting deficiency are:

(1) Severe liver disease, as in toxic or infectious hepatitis or cirrhosis. Vitamin K, fat- or water-soluble, is only occasionally effective in correcting the coagulation defect, but it should be given a cautious trial, with the awareness that large doses may actually aggravate liver disease.

(2) Biliary obstruction and biliary fistulas. Since fat-soluble vitamin K requires the presence of bile (or bile salts) for absorption from the intestine, 300 mg. of Ox Bile Extract, NF, or 500 mg. of Dehydrocholic Acid, USP should be given with each oral dose of vitamin K_1; or one of the water-soluble vitamin K preparations should be administered either orally or parenterally.

(3) Small bowel disorders (such as malabsorption syndromes, and disorders following small bowel surgery). These impair absorption of the bile-acid - vitamin K complex. Parenteral therapy with any vitamin K preparation is preferred.

(4) Interference with the synthesis of prothrombin by the coumarin and indandione anticoagulants and by other drugs. Vitamin K_1 (but not K_3, K_4 or K_5) raises the plasma prothrombin to normal levels within about four hours; and it is useful in preoperative preparation of patients on oral anticoagulants. If anticoagulants are to be resumed after surgery, vitamin K_1 (about 5 mg. orally) should be given initially, with subsequent doses based on prothrombin determinations. Doses greater than 20 mg. intravenously render the patient refractory to further anticoagulant therapy for days or even weeks, and are generally contraindicated. For immediate correction of the hypoprothrombinemia the patient should be transfused with fresh banked blood. Prolonged or excessive use of salicylates may occasionally produce hypoprothrombinemia. Prolonged oral administration of neomycin, kanamycin, broad-spectrum antibiotics, sulfonamides and nitrofurans, by eliminating the normal intestinal flora, may interfere with vitamin K synthesis in the intestines.

(5) Neonatal hypoprothrombinemia has been attributed to poor diet, poor absorption or impaired utilization of vitamin K in the mother. This condition is seldom seen now because of the routine prophylactic administration of water-soluble vitamin K to the newborn. A single parenteral dose of 1 mg. is sufficient; doses in excess of 5 mg. in either mother or infant can lead to brain damage in premature and full-term infants. Special caution is also necessary in infants (and adults) with primaquine sensitivity of the red blood cells. In these patients, certain drugs, including vitamin K in large doses, may cause hemolysis and, in the newborn period, brain damage.

VITAMIN K PREPARATIONS - The following are the principal vitamin K preparations. The various preparations of vitamins K_3, K_4 and K_5 are much less expensive than those of vitamin K_1.

Vitamin K_1 (Phytonadione, USP), fat-soluble
Mephyton (Merck); oral and parenteral
Aqua-Mephyton (Merck); parenteral only
Konakion (Roche); oral and parenteral

Vitamin K_3 (Menadione, USP), fat-soluble
(Many brands)
(Menadione Sodium Bisulfite, USP), water-soluble
Hykinone (Abbott); oral and parenteral

Vitamin K_3 (Menadiol Sodium Diphosphate), water-soluble
Kappadione (Abbott); parenteral only
Vitamin K Analogue (Upjohn); parenteral only
Synkayvite (Roche); oral and parenteral

Vitamin K_5 (4-Amino-2-methyl-1-naphthol HCl), water-soluble
Synkamin (Parke, Davis); oral and parenteral

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